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Original Research Article

Helicobacter Pylori as a Contributory Factor in Gallstone Disease: A Cross-Sectional Observational Study

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Abstract

Background: Gallstone disease is among the commonest surgical disorders of the digestive tract, yet its classical risk factors do not fully account for who develops stones. Helicobacter pylori, long established as a gastric pathogen, has increasingly been recovered from bile and gallbladder tissue, raising the possibility that it contributes to lithogenesis. We examined how often H. pylori is present in patients with gallstone disease and whether its presence relates to stone composition and clinical features.

Methods: This cross-sectional observational study enrolled 85 adults with ultrasonographically proven cholelithiasis admitted for elective cholecystectomy at a tertiary teaching hospital in Jaipur. Before surgery every patient underwent upper gastrointestinal endoscopy with a dry rapid urease test (RUT) on antral biopsy; infection was additionally assessed by serum IgG, stool antigen, bile antigen and gallbladder mucosal histopathology. Stones retrieved at operation were typed biochemically. Associations were tested with the chi-square or Fisher exact test, with $p < 0.05$ considered significant.

Results: The mean age was 42.8 ± 11.6 years and women predominated (68.2%; $p = 0.001$). Gastric RUT was positive in 56.5% of patients, serum IgG in 63.5%, stool antigen in 44.7%, bile antigen in 30.6% and gallbladder histopathology in only 9.4%. Cholesterol stones were commonest (61.2%). RUT positivity was higher among patients with cholesterol stones (65.4%) than pigment (42.9%) or mixed (42.1%) stones, a difference that fell just short of significance ($p = 0.054$). Infection was not associated with stone number ($p = 0.396$) or clinical category ($p = 0.734$). Against RUT, serum IgG was sensitive (85.4%) but less specific, whereas histopathology was highly specific but insensitive (14.6%).

Conclusion: H. pylori is common in patients with gallstone disease and shows a consistent trend toward cholesterol stones, suggesting a contributory rather than causal role. Rapid urease testing and serology outperform conventional histopathology for detection. Larger, molecular-based studies are needed to confirm causality.

Keywords: Helicobacter pylori; cholelithiasis; gallstones; rapid urease test; cholesterol stones; cholecystitis.
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Introduction

Gallstone disease is one of the most familiar problems a general surgeon encounters, and one of the more expensive for any health system to manage. It accounts for a large share of digestive-tract admissions worldwide [1,2] and, despite better imaging and the near-universal shift to laparoscopic surgery, still generates on the order of three-quarters of a million cholecystectomies each year in the United States alone [3]. What makes the condition particularly intriguing is how unevenly it is distributed. Prevalence reaches roughly 10% of adults in the United States and approaches half of all adults in some Native American populations, sits around 14% in parts of Italy, and falls below 4% in Japanese men [4–7]. Differences of that magnitude point to a tangled mix of genetic, dietary, metabolic and possibly infectious influences rather than to any single cause. For

decades the explanation for stone formation has rested on three pillars — cholesterol supersaturation of bile, sluggish gallbladder emptying and the nucleation of cholesterol crystals — all modulated by age, female sex, pregnancy, obesity and diabetes. These factors are real and important, but they leave a good deal of the variation unexplained, which has kept the search open for additional contributors.

One candidate that has drawn growing attention is Helicobacter pylori. This Gram-negative, microaerophilic organism is best known for colonising the stomach and driving chronic gastritis, peptic ulceration and gastric malignancy [8], but its influence appears to extend well beyond the stomach. Most relevant here is the hepatobiliary tract. The long-held assumption that bile is sterile was overturned when Kawaguchi and colleagues demonstrated H. pylori within gallbladder mucosa in 1996 [9], and a steady stream of studies since has identified Helicobacter DNA and antigens in bile, gallstones and gallbladder tissue, often at higher rates in patients with stones than in those without [10,11].

How the organism might promote stone formation is biologically plausible. Persistent infection could inflame the gallbladder lining, alter mucin and bile composition, and slow gallbladder emptying, while bacterial urease may shift local pH enough to encourage precipitation of bile constituents. Whether such findings reflect a genuine causal contribution or merely colonisation of an already-diseased gallbladder remains debated. Against this background, we set out to measure the prevalence of H. pylori in patients with gallstone disease and to test whether its presence was associated with stone composition, stone burden and clinical presentation.

Materials and Methods

This cross-sectional observational study was carried out in the Department of General Surgery of a tertiary teaching hospital in Jaipur over approximately eighteen months, after clearance from the institutional ethics committee. The study population comprised consecutive adults admitted for elective cholecystectomy whose gallstones had been confirmed on ultrasonography. Patients younger than 18 years, those unfit for surgery, and anyone with a previous gastrectomy, cholecystectomy or course of H. pylori eradication were excluded, as were patients in whom preoperative endoscopy could not be performed. Written informed consent was obtained from every participant. The sample size was derived from the standard formula for a single proportion, taking the prevalence of gallstone disease as 15%, an allowable error of 10% and a 99% confidence level ($Z\alpha/2 = 2.58$), which yielded a requirement of 85 patients.

Each patient underwent upper gastrointestinal endoscopy before surgery, during which antral mucosal biopsies were taken for a dry rapid urease test by the slide method. The tissue was placed on a clean glass slide with a drop of normal saline and covered, and the reaction was read between five and twenty minutes; a colour change from yellow to lilac or blue was taken as evidence of H. pylori in the gastric antrum. To build a fuller picture of infection status, H. pylori was additionally assessed serologically (serum IgG), in stool (faecal antigen), in bile (antigen) and on gallbladder mucosa by Giemsa-stained histopathology.

Cholecystectomy was completed by the open or laparoscopic route as clinically appropriate, and the retrieved stones were sent for biochemical analysis and classified as cholesterol, pigment or mixed. Ultrasonographic features, endoscopic findings, stone characteristics and infection status were then collated. Data were analysed in SPSS: categorical variables were summarised as frequencies and compared using the chi-square test, with Fisher's exact test where expected counts were small, and continuous variables as mean ± standard deviation or median with interquartile range according to their distribution (Shapiro–Wilk test). A two-sided p value below 0.05 was treated as significant.

Results

The 85 patients had a mean age of 42.8 ± 11.6 years (range 19–68), and nearly three-quarters were younger than 50. Women clearly outnumbered men, accounting for 68.2% of the cohort against 31.8% — a male-to-female ratio of 1:2.15 that was statistically significant ($p = 0.001$). Right upper quadrant pain was universal, and nausea, fatty-food intolerance and vomiting were each reported by roughly half the patients. Just over half were classified as symptomatic cholelithiasis (56.5%), with acute (25.9%) and chronic (14.1%) cholecystitis accounting for most of the remainder, and metabolic comorbidity — hypertension, obesity, diabetes and dyslipidaemia — was common (Table 1).

Table 1: Demographic and clinical characteristics of the study population (n = 85)

Characteristic	n (%)
Mean age, years (± SD)	42.8 ± 11.6
18–40 years	36 (42.3)
41–60 years	41 (48.2)
> 60 years	8 (9.4)
Female	58 (68.2)
Male	27 (31.8)
Right upper quadrant pain	85 (100)
Nausea	52 (61.2)
Dyspepsia / fatty-food intolerance	46 (54.1)
Symptomatic cholelithiasis	48 (56.5)
Acute cholecystitis	22 (25.9)
Chronic cholecystitis	12 (14.1)
Hypertension	24 (28.2)
Obesity (BMI > 30)	22 (25.9)
Diabetes mellitus	18 (21.2)

Ultrasonography showed a thickened gallbladder wall in half the cohort (mild in 32.9%, marked in 17.6%) and a sonographic Murphy's sign in 40.0%, indicating that inflammatory change was common at presentation. Biochemically, cholesterol stones dominated (61.2%), followed by mixed (22.4%) and pigment (16.5%) stones; two-thirds of patients had multiple calculi and the mean stone diameter was 12.4 ± 6.8 mm. Endoscopy was abnormal in most patients, antral gastritis being the leading finding (32.9%) and only 37.6% of studies reported as normal. The yield of H. pylori varied widely with the test used (Table 2). Serum IgG was positive in 63.5% of patients and gastric RUT in 56.5%, the latter strongly significant ($p < 0.001$). Stool antigen (44.7%, $p = 0.003$) and bile antigen (30.6%, $p = 0.008$) were positive less often, and gallbladder histopathology least of all, at just 9.4% ($p = 0.124$). Among RUT-positive patients the reaction was strong (under 30 minutes) in 25.9%, moderate in 21.2% and weak in 9.4%, suggesting an appreciable bacterial load in many.

Table 2: Detection of H. pylori by different methods (n = 85)

Detection method	Positive, n (%)	p-value
Serum H. pylori IgG antibody	54 (63.5)	—
Gastric biopsy RUT (dry slide)	48 (56.5)	<0.001
Stool antigen (HpSA)	38 (44.7)	0.003
Bile H. pylori antigen	26 (30.6)	0.008
Gallbladder histopathology (Giemsa)	8 (9.4)	0.124

The most clinically interesting signal concerned stone composition (Table 3). H. pylori positivity by RUT was highest in patients with cholesterol stones (65.4%) and considerably lower in those with pigment (42.9%) or mixed (42.1%) stones. The difference was suggestive but stopped just short of conventional significance ($\chi^2 = 5.84$, $p = 0.054$).

Table 3: Association of gastric RUT positivity with stone biochemistry (n = 85)

Stone type	Total, n (%)	RUT-positive, n (%)	p-value
Cholesterol	52 (61.2)	34 (65.4)	0.054
Pigment	14 (16.5)	6 (42.9)	
Mixed	19 (22.4)	8 (42.1)	

Infection bore no relationship to the number of stones (50.0% positive with single versus 59.6% with multiple stones; $p = 0.396$), nor to the clinical category of disease ($p = 0.734$), even though positivity was numerically higher in acute and chronic cholecystitis than in incidental cases. When the four ancillary tests were judged against gastric RUT as the reference standard (Table 4), serum IgG proved sensitive but only moderately specific, stool antigen offered the best overall agreement ($\kappa = 0.54$), bile antigen was specific but insensitive, and gallbladder histopathology, though highly specific, missed most infections ($\kappa = 0.14$).

Table 4: Diagnostic performance of ancillary tests against gastric RUT (n = 85)

Test	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)	κ
Serum IgG	85.4	62.2	74.1	76.7	75.3	0.49
Stool antigen	68.8	86.5	86.8	68.1	76.5	0.54
Bile antigen	47.9	91.9	88.5	57.6	67.1	0.38
GB histopathology	14.6	97.3	87.5	46.8	50.6	0.14

Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; Acc = accuracy; κ = Cohen's kappa (agreement: <0.20 poor, 0.21–0.40 fair, 0.41–0.60 moderate).

Discussion

Taken together, our findings reinforce a now-familiar picture: H. pylori turns up often in people with gallstones, but its role looks supportive rather than decisive. More than half of our patients carried active gastric infection on rapid urease testing and nearly two-thirds were seropositive — figures that sit comfortably alongside the 56% RUT positivity reported by Sai Anurag and colleagues in a comparable Indian cohort, and with the positive, independent associations described in the large Japanese and Chinese surveys of Takahashi and Zhang [12,13,14]. The demographic profile was equally unsurprising: a middle-aged population centred in the fifth decade and a pronounced female excess, both long-recognised features of gallstone disease and both consistent with the oestrogen-related lithogenicity that underlies the sex difference.

The most thought-provoking result was the gradient across stone types. Cholesterol stones, which made up the bulk of our specimens, carried the highest infection rate at 65.4%, well above the rates seen with pigment or mixed stones. That the comparison landed at $p = 0.054$ — tantalisingly close to significance in a sample of this size — is itself worth dwelling on, because the direction fits the proposed biology rather neatly.

If chronic H. pylori infection does inflame the gallbladder, thicken its mucin and slow its emptying, the downstream effect would be precisely the cholesterol supersaturation and crystal nucleation that produce cholesterol stones. Lee, Takahashi and Zhang have all argued along these lines, suggesting that infection-driven inflammation alters bile composition and motility in ways that favour stone formation [10,13,14]. Our data are consistent with that mechanism without, on their own, proving it.

A second clear message concerns how the organism is best detected. Positivity fell steadily as we moved from the stomach outward — 56.5% on gastric RUT, 30.6% in bile and only 9.4% on gallbladder histopathology. The poor yield of Giemsa-stained tissue echoes Rathi and colleagues, who found H. pylori in just one gallbladder specimen using conventional staining and cautioned that, without immunohistochemistry or PCR, such methods badly underestimate colonisation [15]. Guraya and Tajeddin reached similar conclusions, with molecular techniques uncovering the organism where culture and staining failed [16,17]. The practical implication is plain: a negative histopathology result should not be read as absence of infection, and credible future work in this area will need molecular tools. The high burden of gastritis we observed — abnormal endoscopy in nearly two-thirds of patients, antral gastritis most often — lends indirect support to the idea that the stomach acts as the reservoir from which the biliary tree is seeded. Attaallah, Helaly and Sabbaghian have each made this argument, noting the frequent coexistence of gastric and gallbladder infection and proposing spread from the stomach to the biliary system [11,18,19]. Our endoscopic findings fit that narrative, even if they cannot prove the route.

Where the data were unequivocally negative, they were informative too. Infection showed no association with the number of stones or with clinical category, which suggests that whatever role H. pylori plays lies near the start of the process — in initiating lithogenesis — rather than in determining how many stones ultimately form or how the disease declares itself. The pooled analysis by Cen and colleagues, which found a robust association between gallbladder H. pylori and both cholecystitis and cholelithiasis, and a large retrospective Chinese series that likewise tied infection to gallbladder disease, are both consistent with a contributory effect of this kind [20,21].

These conclusions must be read against the study's limitations. With 85 patients, a modest association such as the cholesterol-stone signal was always likely to hover around rather than cross the significance threshold. We relied on a dry RUT and conventional staining and did not use PCR, almost certainly underestimating gallbladder colonisation. The cross-sectional design cannot establish causation, and the absence of a stone-free control group limits comparison. Finally, the metabolic comorbidities so common in this cohort are themselves lithogenic and could confound any infection–stone relationship.

Conclusion

In this cohort of patients with gallstone disease, H. pylori infection was common and showed a consistent, if not quite significant, tendency to

accompany cholesterol stones — the very stones whose formation its proposed mechanisms would best explain. The organism was far more readily detected in the stomach than in the gallbladder, and rapid urease testing and serology clearly outperformed histopathology. Rather than a sole cause, H. pylori is best regarded as one modifiable thread in the multifactorial fabric of gallstone disease. Whether eradicating it can actually lower the risk or recurrence of stones is the question that matters next, and answering it will require larger, controlled, molecular-based studies designed with that endpoint in mind.

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